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(54) **Title of the Invention:**
TERFENADINE-CONTAINING TABLET PREPARATION

(57) **Abstract:**

Object

To provide a terfenadine-containing tablet preparation which can be readily prepared, quickly disintegrates in the stomach when taken orally, and whose active ingredient is rapidly absorbed from the digestive tract.

Means for Solution

This terfenadine-containing tablet preparation comprises:

(a)	terfenadine	1 weight part
(b)	lactose and/or corn starch	2.30 to 2.40 weight parts
(c)	low-substituted hydroxypropyl cellulose	0.45 to 0.55 weight part
(d)	precipitated calcium carbonate	0.95 to 1.05 weight parts
(e)	hydroxypropyl cellulose	0.10 to 0.15 weight part
(f)	magnesium stearate	0.04 to 0.06 weight part

Claims:

Claim 1 A terfenadine-containing tablet preparation, comprising:

(a) terfenadine	1 weight part
(b) lactose and/or corn starch	2.30 to 2.40 weight parts
(c) low-substituted hydroxypropyl cellulose	0.45 to 0.55 weight part
(d) precipitated calcium carbonate	0.95 to 1.05 weight parts
(e) hydroxypropyl cellulose	0.10 to 0.15 weight part
(f) magnesium stearate	0.04 to 0.06 weight part

Claim 2 A terfenadine-containing tablet preparation, comprising:

(a) terfenadine	1 weight part
(b) lactose	1.30 to 1.40 weight parts
corn starch	0.95 to 1.05 weight parts
(c) low-substituted hydroxypropyl cellulose	0.45 to 0.55 weight part
(d) precipitated calcium carbonate	0.95 to 1.05 weight parts
(e) hydroxypropyl cellulose	0.10 to 0.15 weight part
(f) magnesium stearate	0.04 to 0.06 weight part

Claim 3 A 300-mg terfenadine-containing tablet preparation, comprising:

(a) terfenadine	60 mg
(b) lactose	80 mg
corn starch	59 mg
(c) low-substituted hydroxypropyl cellulose	30 mg
(d) precipitated calcium carbonate	60 mg
(e) hydroxypropyl cellulose	8 mg
(f) magnesium stearate	3 mg

Detailed Description of the Invention

[0001]

Technological Field to which the Invention Belongs

The present invention relates to a terfenadine-containing tablet preparation, and more particularly relates to a tablet preparation whose active ingredient is terfenadine and which has excellent bioavailability.

[0002]

Prior Art

Terfenadine (INN), whose chemical name is (±)-α-(p-tert-butylphenyl)-4-(hydroxydiphenylmethyl)-1-piperidinebutanol, is a piperidinoalkanol derivative-based antiallergic drug. Terfenadine is an antiallergic drug having a specific H_1-receptor antagonist action and an inhibitory effect on chemical mediator release, and is used clinically for the treatment of allergic disorders such as bronchial asthma, allergic rhinitis, urticaria, and itching brought on by skin disease (eczema/dermatitis and dermal pruritus). Terfenadine itself is in the form of crystals or a crystalline powder, and is only slightly soluble in water, so various preparations have been studied in an effort to improve the efficient and instantaneous absorption of terfenadine after oral administration, as well as its bioavailability. For instance, Japanese Laid-Open Patent Application H1-128924 discusses investigation into therapeutically inert additives that are added all together in the production of a terfenadine preparation, and states that when specific amounts of a nonionic or cationic surfactant and calcium carbonate were added in a solubility test, the release of terfenadine from the preparation was excellent. Therefore, terfenadine preparations that are currently seeing clinical use contain polyethylene glycol 400 (Macrogol 400), which is the nonionic surfactant referred to in the above-mentioned patent application.

[0003]

Problems which the Invention is Intended to Solve

The inventors investigated preparations with which a terfenadine-containing tablet preparation can be readily prepared, quickly disintegrates in the stomach when the tablet is taken orally, and whose active ingredient (terfenadine) can be released from the preparation and therefore is rapidly absorbed from the digestive tract. As a result, the inventors made the new discovery that when tablets are prepared by combining terfenadine with specific components in specific proportions, even when selected from among the various components that have ordinarily been used in the past for such preparations, a preparation can be easily produced, the tablets readily disintegrate, and the terfenadine contained therein is released favorably.

[0004]

Means Used to Solve the Above-Mentioned Problems

Specifically, the present invention provides a terfenadine-containing tablet preparation comprising:

(a)	terfenadine	1 weight part
(b)	lactose and/or corn starch	2.30 to 2.40 weight parts
(c)	low-substituted hydroxypropyl cellulose	0.45 to 0.55 weight part
(d)	precipitated calcium carbonate	0.95 to 1.05 weight parts
(e)	hydroxypropyl cellulose	0.10 to 0.15 weight part
(f)	magnesium stearate	0.04 to 0.06 weight part

[0005]

Embodiments of the Invention

As above, the present invention is characterized in that specific components selected from among the fillers, disintegrants, binders, and lubricants ordinarily used as optional additives, particularly in the field of pharmaceutical preparations, are blended in specific proportions. Specifically, examples of conventional fillers include microcrystalline cellulose, α-cellulose, crosslinked carboxymethyl cellulose sodium, derivatives of these, and other such celluloses; and lactose, corn starch, hydroxypropyl starch, carboxymethyl starch, crosslinked starch, amylose, and other such polysaccharides. Examples of binders include pregelatinized starch, povidone, methyl cellulose, hydroxypropyl cellulose, and hydroxypropylmethyl cellulose. Examples of disintegrants include starch, gelatin, crystalline cellulose, low-substituted hydroxypropyl cellulose, carboxymethyl cellulose sodium, calcium carbonate, and sodium hydrogen carbonate. Examples of lubricants include talc, magnesium stearate, calcium stearate, zinc stearate, and stearic acid. However, investigation conducted by the inventors has revealed that when terfenadine is formulated into tablets, when the characteristics of the active ingredient terfenadine as a powder are taken into account, best results will be obtained when lactose and corn starch are both used as fillers in specific proportions, namely, 3 weight parts corn starch per 4 weight parts lactose, low-substituted hydroxypropyl cellulose and precipitated calcium carbonate are used in a specific number of weight parts as disintegrants, hydroxypropyl cellulose is used as a binder, and magnesium stearate is used as a lubricant, each in a specific number of weight parts.

[0006]

Therefore, a preferred terfenadine-containing tablet preparation of the present invention is a terfenadine-containing tablet preparation comprising:

(a)	terfenadine	1 weight part
(b)	lactose	1.30 to 1.40 weight parts
	corn starch	0.95 to 1.05 weight parts
(c)	low-substituted hydroxypropyl cellulose	0.45 to 0.55 weight part
(d)	precipitated calcium carbonate	0.95 to 1.05 weight parts
(e)	hydroxypropyl cellulose	0.10 to 0.15 weight part
(f)	magnesium stearate	0.04 to 0.06 weight part

[0007]

Taking into account the amounts used clinically for the treatment of allergic disorders such as bronchial asthma, allergic rhinitis, urticaria, and itching brought on by skin disease (eczema/dermatitis and dermal pruritus), when a 300 mg tablet containing 60 mg of terfenadine is prepared, the best specific composition is as follows:

(a)	terfenadine	60 mg
(b)	lactose	80 mg
	corn starch	59 mg
(c)	low-substituted hydroxypropyl cellulose	30 mg
(d)	precipitated calcium carbonate	60 mg
(e)	hydroxypropyl cellulose	8 mg
(f)	magnesium stearate	3 mg

[0008]

The terfenadine-containing tablet preparation of the present invention is characterized in that specific components are added in specific proportions, as discussed above, and it has become clear that there is no need at all to add the nonionic surfactant disclosed in Japanese Laid-Open Patent Application H1-128924, which previously proposed a terfenadine-containing preparation. Specifically, a 300 mg tablet containing 60 mg of terfenadine on the basis of the particularly favorable specific composition can combine a number of disintegrants as needed, but it has been found that a particularly favorable combination is low-substituted hydroxypropyl cellulose and precipitated calcium carbonate. When each of these was used in a specific number of weight parts and the product subjected to a tablet preparation disintegration test (elution test) and a terfenadine absorption test on humans (both discussed below), the results were substantially consistent with those obtained with preparations of prior art.

[0009]

A tablet used in actual clinical practice is manufactured as follows, for example, on the basis of the specific tablet composition of the present invention. Specifically, any known preparation method can be employed, such as dry mixing or wet mixing, but more specifically, terfenadine, lactose, corn starch, low-substituted hydroxypropyl cellulose, precipitated calcium carbonate, and hydroxypropyl cellulose are mixed, water is then added and kneaded in, and this product is granulated. The granulated product is dried for 16 hours at 45°C, graded, and then mixed with magnesium stearate and molded into tablets.

[0010]

Working Examples

The results of an elution test of tablets produced according to the terfenadine-containing composition of the present invention, and an absorption test of these tablets on humans, are given below.

Production of the preparation

Terfenadine, lactose, corn starch, low-substituted hydroxypropyl cellulose, precipitated calcium carbonate, and hydroxypropyl cellulose were mixed in a high-speed mixer in the following amounts.

terfenadine	420 g
lactose	560 g
corn starch	420 g
low-substituted hydroxypropyl cellulose	210 g
precipitated calcium carbonate	420 g
hydroxypropyl cellulose	56 g
magnesium stearate	21 g
	total: 2100 g [sic]

A suitable amount of purified water was then added to this mixture and kneaded. This product was granulated in a power mill and dried (16 hours at 45°C in a flow-through air dryer), after which the dried product was sifted (30 mesh) and graded. Magnesium stearate that had been sifted at 60 mesh was then added, and the components were mixed for 5 minutes in a V-shaped mixer. The mixture thus obtained was molded into tablets using a pestle with a diameter of 9.0 mm, which gave a tablet of 300 mg (containing 60 mg terfenadine).

[0011]

Test Example: Elution Test

Six of the terfenadine-containing tablets prepared above were subjected to an elution test at 37°C, using Japanese Pharmacopoeia liquid No. 1, according to the elution test set forth in the Japanese Pharmacopoeia. As a control, an elution test was conducted under the same conditions using Triludan™ tablets (Marion Merrell Dow), which are available on the market as tablets containing 60 mg of terfenadine. As a result, no significant difference in the extent of terfenadine elution was noted between the tablets produced in accordance with the composition of the present invention and the Triludan tablets used as control. Therefore, when orally administered to humans, the tablet of the present invention quickly disintegrates in the stomach, and the terfenadine is eluted and efficiently absorbed.

[0012]

Effect of the Invention

As discussed above, the terfenadine-containing tablet preparation of the present invention is characterized by being prepared by mixing certain specific components, which may be selected from among fillers, disintegrants, and lubricants, for example, in specific proportions, taking into account the powder characteristics of terfenadine. In particular, when the terfenadine is formulated into tablets, if lactose and corn starch are both used as fillers in specific proportions (number of weight parts), low-substituted hydroxypropyl cellulose and precipitated calcium carbonate are used in a specific number of weight parts as disintegrants, and magnesium stearate is used as a lubricant in a specific number of weight parts, the tablets will disintegrate well, which is advantageous in that absorption will be good in the body after administration. These advantages are obtained as a result of blending the specific components in specific proportions in accordance with the present invention, and the present invention can therefore be considered to be extremely useful.